AMENDMENTS TO THE SPECIFICATION

Please amend the specification on page 1, line 4 through line 13 as follows:

The inventions relate to a method and an apparatus of preparing a solution containing biological components, particularly a solution containing biological components ~~with changed composition~~ obtained by isolating biological molecules [[of]] such as proteins extracted from human serum, urine, or the like. Specifically ~~Specially~~, the invention relates to a method and an apparatus for ~~of a solution of biological components with changed composition by~~ removing biological components inhibiting detection of trace components, particularly removing proteins with high molecular weights with the ~~for a~~ purpose of carrying ~~to carry~~ out clinical proteome analysis.

Please amend the specification on page 1, line 15 through line 24 as follows:

Recently, proteome analysis research proteomics has begun to draw attention as postgenome research. Since it is a very likely supposition that proteins, gene products, are more directly linked with syndromes of diseases than genes ~~gene~~, it has been highly expected that research findings and achievements in [[of]] proteome analysis which [[of]] thoroughly investigates ~~investigating~~ proteins can widely be applicable for diagnosis and medical care. Moreover, it is highly possible to find many proteins causing diseases and factors relevant to diseases, which cannot be found by genome analysis.

Please amend the specification on page 1, line 25 through page 2, line 2 as follows:

High speed structural analysis is made possible by MS (mass spectrometer) and technically it has greatly contributed to rapid advancement of proteome analysis. Practical ~~and practical~~ application of MALDI-TOF-MS (matrix assisted laser desorption ionization time-of-flight mass spectrometry) has enabled ultramicroanalysis of polypeptides to be performed at a

high throughput~~, and that~~. This makes it possible to identify even trace proteins which have not been [[be]] detected conventionally and accordingly becomes a powerful tool for searching factors relevant to diseases.

Please amend the specification on page 2, line 3 through line 17 as follows:

The first purpose of clinical application of the proteome analysis is to find biomarker proteins induced or eliminated by diseases. The biomarker behaves in relation to symptoms of diseases, so that it [[is]] can be a marker for diagnosis and also highly possibly becomes a target for producing pharmaceuticals. That is, since the findings and achievements of proteome analysis are highly possibly applicable to find a diagnosis marker and a target for producing pharmaceuticals rather than a specified gene, it can be said that proteome analysis becomes a key technology for diagnosis and medical care in the postgenome age ~~and~~. Also, since the identified biomarker directly brings profits to patients, that is, evaluation of response to the pharmaceuticals and expectation of side effect development, it can be said that this technique plays an important role to promote so-called tailor-made medical care.

Please amend the specification on page 2, line 18 through line 29 as follows:

If ~~In the case~~ proteome analysis is to be introduced in clinical research ~~researches~~, it is required to quickly and reliably analyze a large number of samples and moreover, since each clinical sample is slight in the amount and very precious, it is required to carry out ~~the~~ a highly functional measurement with high resolution, and high sensitivity~~, and highly functional measurement~~. Mass spectrometry has considerably propelled the analysis and the characteristics of mass spectrometers, that is, high sensitivity and high throughput have greatly contributed to the analysis. However, although the techniques and appliances have ~~been~~ improved swiftly, the

present situation does not yet allow one ~~is not yet ready~~ to simply and quickly carry out proteome analysis in a clinical field.

Please amend the specification on page 2, line 19 through page 3, line 7 as follows:

One of the causes is attributed to pretreatment of clinical samples. It is ~~needed~~ necessary to carry out ~~fractionate~~ fractionation and refine the proteins of a clinical sample with a pretreatment ~~as treatment~~ before mass analysis ~~and the~~. The pretreatment ~~treatment~~ still takes several days and the operation of the pretreatment is complicated requiring experience ~~and requires experiences~~ and skills and that become ~~becomes~~ a high obstacle against ~~the~~ clinical ~~application~~ applications. If diagnosis of a disease in the entire body and the ~~symptom~~ control of symptoms are made possible with a small amount of blood and body fluid, this would be ~~it is~~ remarkably useful~~, however~~. However, there are many challenging objects ~~subjects~~ to overcome due to the variation of proteins contained in blood plasma.

Please amend the specification on page 3, line 8 through line 27 as follows:

It is assumed that there are 100,000 or more kinds of human proteins and about 10,000 kinds of proteins are contained in serums and the concentration of the total proteins in the serums is about 60 to 80 mg/mL. The proteins contained in a human serum are albumin (molecular weight: 66 kDa), immunoglobulin (150 to 190 kDa), transferrin (80 kDa), haptoglobin (>85 kDa), and lipoprotein (several 100kDa) and all of them exist respectively in an amount exceeding 1 mg/mL. On the other hand, many of physiological active proteins such as peptide hormones, interleukin, and cytokine regarded to be biomarkers of symptoms and factors relevant to diseases exist in a trace amount lower than 1 ng/mL and the contents are no more than nano to pico level as compared to those of the high content components with high molecular weights. In terms of the size of proteins, 70% or less of [[in]] all kinds of proteins have a molecular weight of 60,000 (60kDa) or lower and the above-mentioned biomarker proteins present in trace

amounts ~~existing in a trace~~ are almost all included in this range (reference to Non-patent Document No. 1). Since these proteins are partially excreted to urine through the [[a]] kidney, not only blood but also urine may be used as a sample.

Please amend the specification on page 4, line 1 through line 16 as follows:

Presently, high performance liquid chromatography (LC) and 2-dimensional electrophoresis (2 dimensional-polyacrylamide gel electrophoresis: 2D-PAGE) have been employed as means of separation and removal of the high molecular weight proteins, however it takes a 1 to 2 of days only for LC and 2D-PAGE operation. The time needed for them is very long as compared with the analysis time, several minutes, for MALDI-TOF-MS and ESI-MS (electrospray ionization mass spectrometry) and the remarkable advantageous point that MS, an analysis means, has a high throughput cannot sufficiently be exhibited in ~~the~~ clinical proteome analysis. Therefore, it must be said that at the present moment, MS is insufficient in practical applications for the purpose of obtaining analysis results within a time as short as possible for diagnosis and medical care in medical treatment fields and it is difficult to use ~~becomes a significant cause of difficulty of utilization of~~ MS for ~~the~~ daily clinical investigations.

Please amend the specification on page 4, line 17 through line 25 as follows:

Therefore, it is expected that promptness of diagnosis of the clinical investigations by clinical proteome analysis may remarkably be improved if the means of removing a portion of all of high molecular weight proteins from a sample is accelerated. Practically, that can be accomplished if a method or an apparatus for removing biological components from ~~of obtaining~~ a biological components-containing solution ~~with a changed composition of biological components~~ while leaving a group of targeted ~~aimed~~ proteins from a small amount of a sample at a high speed are made available in place of the LC and 2D-PAGE techniques.

Please amend the specification on page 4, line 26 through page 5, line 2 as follows:

As already practically utilized products or disclosed techniques for ~~means of~~ removing a main object substance, albumin, there are a carrier (commercialized) in which an affinity ligand such as a blue dye is immobilized, a centrifugal tubular apparatus (commercialized) for fractionating the high molecular weight components by centrifugal filtration, a method of fractionation based on the [[by]] electrophoresis principle, a traditional precipitation method such as ethanol precipitation by Cohn, and a method of fractionation by chromatography (reference to Non-patent Document No. 2).

Please amend the specification on page 5, line 3 through line 10 as follows:

However, they all have problems such as insufficiency of the separation capability, unsuitability for a very small amount of a sample, and contamination of chemical agents which are ~~to be~~ obstacles for mass spectrometry. Particularly, a method of removing albumin as a target solely by adsorption is capable of removing albumin, however it is difficult for the method to remove the high molecular weight components with a molecular weight of 60,000 or higher such as immunoglobulin.

Please amend the specification on page 5, line 19 through line 27 as follows:

If a method or an apparatus capable of solving these problems could be developed, proteome analysis would be performed widely in medical research ~~researches~~ and clinical work fields and it would be ~~is made~~ possible to carry out investigation and diagnosis at a higher speed and a higher precision. Accordingly ~~and accordingly~~, the method or the apparatus would be [[is]] expected to be a powerful tool to investigate cases ~~causes~~ of ~~hardly curable~~ diseases that are difficult to cure for which efficacious medical care ~~caring~~ methods are not yet available or to develop methods of diagnosing these diseases at an [[in]] early stage.

Please amend the specification on page 5, line 28 through line 33 as follows:

As described above, it is needed to remove excess high molecular weight proteins which are ~~to be~~ obstacles to [[in]] clinical proteome analysis. It has been required so far to develop a device having a high separation capability and being more convenient and faster than techniques such as 2D-PAGE and liquid chromatography which are complicated and take a long time.

Please amend the specification on page 6, line 7 through line 18 as follows:

The conditions required for ~~the~~ techniques ~~of~~ aiming at the removal of albumin from blood plasma are that the components of blood plasma are passed at a high speed; that there is not a protein denaturation function; that very fine processing is done for high functionality; and that it is ~~they are~~ not considerably costly. Neither apparatus nor device that can solve the above-mentioned problems and satisfy the above conditions has been made available yet.
[Non-patent Document No.1] Anderson NL, Anderson NG, "The human plasma proteome: history, character, and diagnostic prospects)", proteomics(Molecular & Cellular Proteomics), USA, The American Society for Biochemistry and Molecular Biology, Inc., (2002) vol. 1, p845-867.

Please amend the specification on page 7, line 2 through line 8 as follows:

In view of the above state of the art, it is an object of the inventions to provide a method and an apparatus for removing biological components from ~~of preparing~~ a biological components-containing solution so as to be ~~with a composition of changed biological components~~ suitable for proteome analysis by separating and removing excess high molecular weight proteins which are ~~to be~~ obstacles at the time of clinical proteome analysis from the [[a]] biological components-containing solution.

Please amend the specification on page 12, line 21 through line 24 as follows:

9. The apparatus for preparing a solution as described above which includes ~~in the claim 29, comprising~~ a liquid flow-out path to be joined to a liquid chromatograph, an electrophoretic apparatus, or a mass spectrometer.